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RESEARCH ARTICLE

The role of diet in multiple sclerosis onset and course: results from a nationwide retrospective birth-year cohort

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Abstract

Objective: To examine (1) the association between childhood diet and developing MS, age of onset and onset type and (2) the association between diet at age 50 and disability and MRI volumes in people with MS (PwMS). **Methods**: The study enrolled 361 PwMS born in 1966 and 125 age- and sex-matched healthy controls (HCs). Information on individual dietary components (fruit, vegetables, red meat, oily fish, whole-grain bread and candy, snacks and fast food) and MS risk factors at the age of 10 and 50 years were collected using questionnaires. Overall diet quality score was calculated for each participant. Multivariable regression analyses were used to evaluate the association between diet at childhood and developing MS, age of onset and onset type and to evaluate diet at age 50, disability and MRI outcomes. **Results**: Poorer overall diet quality and individual dietary components during childhood (less whole-grain bread, more candy, snacks and fast food and oily fish) were associated with developing MS and onset type (all $p < 0.05$), but not with the age of onset. Fruit consumption at age 50 was associated with lower disability (Q3 vs. Q1: −0.51; 95% CI: −0.89 to −0.13). Furthermore, several individual dietary components at age 50 were associated with MRI volumetric measures. Higher-diet quality at age 50 was only associated with lower lesion volumes in PwMS (Q2 vs. Q1: −0.3 mL; 95% CI: −0.5 to −0.02). **Interpretation**: We demonstrate significant associations between dietary factors in childhood and developing MS, age of onset and onset type and between dietary factors at age 50 and disability and MRI-derived volumes.

Introduction

Multiple sclerosis (MS) is a complex disease of the CNS with a highly variable clinical expression, disease course and age of onset.[1] Despite substantial efforts, the aetiology of MS remains poorly understood. Besides genetic factors that only explain a fraction of variance in MS risk between individuals, environmental factors are important contributors to MS susceptibility and disease course, including smoking, high geographical latitude, low vitamin D levels, obesity and Epstein–Barr virus (EBV).[2–5] Since early ecological studies supported a role for diet in MS,[6] nutrition has been proposed as one of the possible environmental factors involved in MS pathogenesis. Furthermore, results from preclinical studies have prompted interest in the possible disease-modifying effect of diet. Nonetheless, currently, insufficient evidence exists to recommend a specific diet to people with MS (PwMS) in clinical practice.

Several studies have assessed the relationship between dietary patterns and MS disease course,[7–9] though strong consistent evidence is lacking. A large cross-sectional survey study suggested an association between a healthy diet and lower patient-reported disability and symptom burden.[8] Furthermore, two imaging studies have been conducted

which link unhealthier diet preferences (lower diet scores) to higher T2 lesion volume (LV) accrual over a 5-year follow-up period,[10] and higher adherence to Mediterranean diet (MIND; Mediterranean-Dietary Approach to Stop Hypertension Intervention for Neurodegenerative Delay) with higher normalized thalamic volume in people with early MS.[11] However, population-based cohorts exploring the association between diet and multiple regional MRI volumes in both PwMS and controls are lacking.

The impact of diet on disease outcome in PwMS may already be of importance in early life, given that childhood is a potentially susceptible window of exposure, as has been suggested for obesity and sun exposure.[12–14] However, to date, only a few studies exist on the relationship between diet in early life and adult-onset MS. A recent study showed that higher consumption of fruit, yoghurt and legumes during childhood and young adulthood is associated with a lower probability of adult-onset MS,[15] while another study reported a protective effect against developing MS with higher intake of fish, poultry, yoghurt, butter, fruit and vegetables during adolescence.[16] Furthermore, a large prospective study including women from Nurses' Health Study I and II found an inverse association between dietary PUFA intake and MS risk.[17] Another study utilizing Nurses' Health Study I and II reported a positive association between intake of whole milk and MS risk.[18] Thus far, no data exist on the effects of childhood diet on age of first MS-related symptoms and MS subtype at onset. Furthermore, prior studies have included participants from different birth years, thereby introducing different dietary trends, availability of nutritional components and nutritional content associated with different time epochs.[19]

Therefore, in a cohort of PwMS of the same birth year (year 1966, mean age 53), we explored (1) the association between childhood diet, including overall diet quality and individual components, and developing MS, age of onset and onset subtype and (2) the association between diet at age 50, including overall diet quality and individual components, and disability and MRI volumetric measures. Project Y is a population-based cross-sectional study of all PwMS born in the Netherlands in the year 1966, which enables us to study phenotypic variability in MS, without the confounding effect of age. By including participants born in the same year, the study reduces the effect of differential exposure to environmental and cultural factors.

Methods

Study population

This study investigated patients and healthy controls (HC) of the Project Y cohort.[20] Project Y is a population-based cross-sectional retrospective birth-year cohort of PwMS and HCs of the same birth year, aiming to identify factors explaining phenotype variability in MS. Project Y patients were all diagnosed with MS according to the 2017 McDonald criteria[21] and born in the Netherlands in 1966. This year was deliberately chosen for several reasons: between the age of 51 and 54, the majority of people who will develop MS will have had their first clinical manifestation; participants will have MS for more than 10 years and most patients are still alive. PwMS were recruited via PwMS associations' flyers and websites, radio, social media outreach, newspaper advertisements, nursing homes and (MS) neurologists from every hospital in the Netherlands.[20] HCs were age and sex-matched (birth year 1965–1967) and were recruited via the aforementioned media channels as well as through the assistance of PwMS. Based on the estimated prevalence of MS in the Netherlands in 2017 and on the total number of people born in 1966, we estimated a maximum of 250 patients eligible for inclusion in the Project Y study.[20] As only a limited number of research questions would require a control group for comparisons, it was decided to include 125 HC.[20] A detailed description of the rationale and study design has been described elsewhere.[20] A total of 367 PwMS and 125 HC completed a study visit between December 2017 and January 2021 at the Amsterdam University Medical Center (Amsterdam UMC), location VUmc. We excluded participants who did not provide information on diet or weight during childhood. The project Y study was approved by the local ethics committee of the Amsterdam UMC, location VUmc. All participants gave written informed consent prior to participation.

Clinical assessment

The 1-day study visit included, among others, functional and static imaging, a neurological and neuropsychological assessment and a detailed interview. A detailed MS history, including among others, date of onset, MS subtype and disease-modifying therapy (DMT), was recorded and reviewed from the patients' medical records. Additional information regarding data collection is provided elsewhere.[20] General disability was assessed by certified raters (doctors-researchers) using the Expanded Disability Status Scale (EDSS). For patients unable or unwilling to travel to the hospital, data were collected by means of a home visit or telephone interview, using a validated EDSS assessment by telephone.[22] In short, patients were asked about their level of disability in each functional system through a standardized phone interview with trained examiners (doctors-researchers). The current body mass index (BMI) was calculated by dividing weight by the square of height.

Dietary information

After the 1-day study visit, participants were asked to complete a set of in-house developed questionnaires, which are described in detail elsewhere.[20] The questionnaire was administered once, and captured lifestyle factors early and later in life among others. Using these questionnaires, dietary intake was assessed by asking participants 'how many times a week did you eat the following foods when you were around 10 and 50 years old' ('vegetables', 'fruit', 'red meat', 'oily fish', 'whole grain bread' and 'fast food, snacks and candy'). For each of the aforementioned dietary components during the age of 10 years, patients and HCs were categorized into three groups according to tertile rankings based on the intake of the food product. Subsequently, we calculated an overall diet quality score for each participant. The diet quality score rewarded points for a high intake of fruit and vegetables, oily fish and whole-grain bread (e.g. individuals in the lowest tertile received a score of 1 and participants in the highest tertile received a score of 3). In contrast, for high intake of red meat, candy and fast food, participants in the lowest tertile received a score of 3 and the highest tertile a score of 1. The overall diet quality score was calculated by adding all component scores and ranged from 6 to 18. The same method was used for the age of 50 years.

Potential confounders

Potential risk factors and confounders such as sun exposure, weight category, smoking behaviour and physical activity at age 10 and age 50 were also recorded using questionnaires. Questions on sun exposure referred to the age of 6–10 years and age 50–52 and included queries on sun exposure during the weekends and holidays (<1, 1–2, 2–3, 3–4 or >4 h). For each season (summer and winter), the middle value (e.g. 1.5 for the answer '1–2' h/day) was used to calculate the average time spent in the sun. Physical activity was assessed by asking the following question: 'at the age of 10 or 50 years, how often did you participate in intensive activities (i.e. soccer, hockey, squash, running) for at least ten minutes?' and 'at the age of 10 or 50 years, how often did you participate in moderately intensive activities (i.e. dancing, badminton, brisk walking) for at least ten minutes?' We calculated cumulative physical activity by summing the number of intensive activities and moderately intensive activities. Weight category was assessed by asking 'what was your body weight like during childhood (6-12 years of age)?'. Participants could choose between the following answers: 'severely underweight', 'underweight', 'normal weight', 'overweight' or 'severely overweight'. The ordinal variable 'weight category' during childhood was dichotomized ('non-overweight' and 'overweight or obese') to avoid a small sample size. Participants were asked about the age at which they first smoked and participants were regrouped into 'smokers' and 'non-smokers' before the age of 12 years (childhood). In addition, participants were categorized into 'current smokers' and 'non-smokers' at the time of sampling.

MRI – image processing

MRI volumetric measures were derived from 3.0 T brain MR imaging (Discovery MR750; GE, Milwaukee, WI) and have previously been quantified for this cohort.[23] For both PwMS and HC, T2 lesion volume (LV) was derived from FLAIR images using lesion masks created by a multi-view conventional neural network.[24] Subsequently, these lesion masks were used to create lesion-filled T1 images using LEAP, which was used to calculate all other MRI volumes.[25] Normalized total brain (*NBV*), total grey-(NGMV) and white matter volumes (NWMV) were calculated with SIENAX (part of FSL 6), using SIENAX V-scaling to normalize for head size. Total normalized deep grey matter (NDGMV) and thalamic volume (NThalV) were measured with FIRST segmentations (FSL 6). Normalized cortical grey matter volume (NCGMV) was calculated by subtracting total deep grey matter masks from total grey matter masks. Normalized cerebellar grey matter volume (NCbV) was calculated using the Harvard-Oxford atlas (part of FSL).[26] Finally, mean upper cervical cord area (MUCCA) was derived from axial slices from the cervical spinal cord segment spanning from the superior voxel of C1 to 30 mm inferior to that point derived from the cerebral 3DT1 sequence, using SCT-deepseg, as previously validated. All volumes were adjusted for head size using SIENAX V-scaling.[27]

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 26.0. Histograms and Q–Q plots were used to assess the normality of distribution. LVs were log-transformed to improve normality. Differences in normally distributed data were analyzed using two-tailed *t* tests or ANOVA. Non-normally distributed data were analyzed using the Mann–Whitney *U* test or Kruskal–Wallis test and were reported with median values and the interquartile range (IQR). Differences between categorical variables were tested for statistical significance using chi-square tests. As our research is hypothesis generating, data were unadjusted for multiple testing.

Childhood diet and MS

The association between individual diet components and overall diet quality score and MS case status was assessed using multivariable logistic regression analysis. For all analyses, two multivariable models were created: model (a) included sex, smoking before the age of 12 years (yes/no) and sun exposure in childhood, while multivariable model (b) included all aforementioned covariates but also physical activity and overweight or obese during childhood (yes/no), unless stated otherwise. We used multivariable linear regression analyses to examine the association between childhood diet (independent variable) and age of first symptom onset, also using onset type as a covariate. Multivariable logistic regression analyses were performed to investigate the association between childhood diet and onset type (relapsing-remitting (RR) onset vs. progressive onset), also adjusting for age at onset.

Diet at age 50 and MS

Multivariable linear regression models examined associations between individual diet components and MRI volumetric measures and disability (EDSS) as well as overall diet quality. Again, two multivariable models were created: model (a) included sex, current smoking status, sun exposure at age 50, disease-modifying therapy (DMT) duration, onset type (relapsing vs. progressive), education and disease duration, whereas multivariable model (b) included all aforementioned covariates but also physical activity and BMI.

Individual diet components and overall diet quality were both assessed as categorical and continuous variables in all regressions; diet categories were tested for linear trends by modelling the intake of each tertile as a continuous variable. Multi-collinearity was assessed using VIF. Statistical significance was assumed for $p < 0.05$ for each individual test. Considering the apparent sex differences in prevalence and clinical course of MS,[28] associations were explored for effect modification by sex. Effect modification by sex was explored if the interaction term (sex × diet measure) was $p < 0.10$.

Results

Demographic and clinical characteristics

A total of 361 patients and 125 HCs were included in the analysis; demographic and clinical data are shown in Table 1. Median age at MS onset was 37.1 years (IQR 28.8–44.2). All global and regional brain measures were lower in MS patients compared to HCs (all $p < 0.001$). Being overweight during childhood was more prevalent in PwMS compared to HCs (PwMS: 12.7% vs. HC: 4.8%, $p = 0.012$). Time spent on moderate to intense physical activity at the age of 50 was lower in PwMS compared to HCs (PwMS: 2.0, IQR 0.0–5.0 vs. HC: 4.0, IQR 2.0–6.0, $p < 0.001$).

Diet composition at childhood

Case status

Oily fish consumption was significantly related to case status: MS was more prevalent among individuals who frequently consumed oily fish during childhood (Table 2; Q3 vs. Q1: multivariable (b) OR: 3.26; 95% CI 1.11–9.58, test for trend $p = 0.221$). Adult-onset MS was less prevalent among individuals with a higher intake of whole-grain bread during childhood (multivariable (b) OR: 0.94, 95% CI 0.88–0.99). Sex interaction was observed in the association between case status and whole-grain bread ($p = 0.072$), overall diet quality ($p = 0.005$) and candy, fast food and snacks ($p = 0.020$). After sex stratification, a higher intake of whole-grain bread during childhood was associated with lower odds of MS (Q3 vs. Q1, multivariable OR: 0.47; 95% CI 0.25–0.88, test for trend $p = 0.022$) in female individuals, but not in males. In males, however, PwMS had a lower diet quality (Q2 vs. Q1, multivariable OR: 0.24; 95% CI 0.082–0.70, test for trend $p = 0.092$) and higher intake of candy fast food and snacks as a child (Q2 vs. Q1, multivariable OR: 3.10; 95% CI 1.22–7.84, test for trend $p = 0.079$) compared to HC, but the test for trend did not reach statistical significance.

Age of first symptom onset

None of the individual dietary products were associated with the age of first symptom onset. Besides, no evidence of a significant association between diet quality and age of onset was observed.

Onset type

Subsequently, the relation between childhood diet and onset type was assessed. No significant association between childhood diet and onset type (relapsing vs. progressive) was observed. However, effect modification by sex was found for the association between fruit intake and onset type. In male PwMS, frequent fruit consumption during childhood (Q3 vs. Q1, multivariable OR: 0.24; 95% CI 0.067–0.85, test for trend $p = 0.021$) was

Table 1. Demographic, clinical and radiological characteristics of people with MS (PwMS) and healthy controls (HC).

Characteristic	MS patients (n = 361)	HC (n = 125)	p value
Cohort characteristics at sampling			
Age, years (mean, SD)	53.1 ± 1.0	52.9 ± 1.2	**0.014**
Age at onset, years (median, IQR)	37.1 (28.8–44.2)	–	–
Unknown, n (%)	1 (0.3)	–	–
Female sex, n (%)	312 (86.4)	116 (93.6)	
Education (median, IQR)[a]	5.0 (5.0–6.0)	6.0 (5.0–6.0)	**0.001**
BMI	26.0 ± 4.8	25.7 ± 3.7	0.410
RRMS, n (%)	206 (99.2)	–	–
SPMS, n (%)	106 (29.4)	–	–
PPMS, n (%)	46 (12.7)	–	–
Unknown MS type, n (%)	3 (0.8)	–	–
EDSS (median, IQR)	4.0 (2.5–5.5)	–	–
Disease-modifying therapy use, total duration, years (median, IQR)	6.1 (2.6–11.7)	–	–
Current smoker, n (%)	54 (15.0)	12 (9.6)	0.134
Unknown, n (%)	2 (0.6)	–	–
MRI volumetric measures at sampling mean SD	N = 234	N = 113	
Normalized total brain volume (NBV)	1483.2 ± 77.6	1535.6 ± 77.2	**<0.001**
Normalized white matter volume (NWMV)	694.5 ± 43.0	714.0 ± 42.3	**<0.001**
Normalized cortical grey matter volume (NCGMV)	755.3 ± 52.1	785.4 ± 42.6	**<0.001**
Normalized deep grey matter volume (NDGMV)	59.1 ± 5.4	63.5 ± 4.9	**<0.001**
Normalized thalamic volume (NThalV)	19.6 ± 2.0	21.4 ± 1.7	**<0.001**
Normalized cerebellar grey matter volume	101.9 ± 13.6	108.4 ± 14.1	**<0.001**
Normalized mean upper cervical cord area (MUCCA)	89.9 ± 13.0	97.1 ± 10.7	**<0.001**
Lesion volume (log-transformed)	2.4 ± 0.8	1.1 ± 0.7	**<0.001**
Childhood age 10			
Smoking ever (yes), n (%)	21 (5.8)	5 (4.0)	0.499
Unknown, n (%)	1 (0.3)	–	–
Sun exposure, hours (median, IQR)	2.5 (1.5–3.5)	2.5 (2.0–3.0)	0.307
Unknown, n (%)	2 (0.6)	1 (0.8)	–
Physical activity, hours (median, IQR)	1.0 (0.5–1.5)	0.8 (0.5–1.5)	0.540
Unknown, n (%)	2 (0.6)	1 (0.8)	–
Overweight (6–12 years), n (%)	46 (12.7)	6 (4.8)	**0.012**
Diet			
Fruit	5.0 (4.0–7.0)	5.0 (4.0–7.0)	0.440
Vegetables	6.0 (5.0–7.0)	6.0 (5.0–7.0)	0.727
Oily fish	1.0 (0.0–1.0)	0.0 (0.0–1.0)	0.330
Red meat	2.0 (0.3–3.8)	2.0 (0.5–4.0)	0.851
Whole-grain bread	5.0 (0.0–7.0)	6.0 (2.5–7.0)	0.051
Snacks, candy and fast food	7.0 (3.0–10.0)	6.0 (3.0–11.0)	0.670
Overall diet quality score (median, IQR)	12.0 (10.0–13.0)	12.0 (11.0–13.0)	0.471
Age 50			
Sun exposure, hours (median, IQR)	2.0 (1.0–2.5)	2.0 (1.5–3.0)	0.076
Physical activity, hours (median, IQR)	2.0 (0.0–5.0)	4.0 (2.0–6.0)	**<0.001**
Diet			
Fruit	6.0 (3.0–7.0)	6.0 (4.0–7.0)	0.224
Vegetables	6.0 (5.0–7.0)	6.0 (5.0–7.0)	0.503
Oily fish	1.0 (0.0–2.0)	1.0 (1.0–1.5)	0.937
Red meat	1.0 (1.0–3.0)	1.0 (1.0–2.0)	0.666
Whole grain bread	6.0 (3.3–7.0)	7.0 (4.0–7.0)	0.107
Snacks, candy and fast food	6.0 (3.0–9.0)	6.0 (4.0–10.3)	0.113
Overall diet quality score (median, IQR)	12.0 (10.0–14.0)	12.0 (10.0–14.0)	0.426

Bold values denote statistical significance at the $p < 0.05$ level.

[a]1 = no education; 2 = primary education; 3 = primary education completed and further education of <2 years; 4 = pre-vocational secondary education; 5 = vocational secondary education; 6 = secondary education (higher general secondary education and pre-university education); 7 = university/post-doctoral.

associated with lower odds of relapsing onset MS, but not in female PwMS.

Diet composition at 50 years of age

Disability

PwMS with higher fruit intake at age 50 had a significantly lower EDSS (Fig. 1; Q3 vs. Q1: multivariable unstd. $B = -0.51$; 95% CI −0.89 to −0.13, test for trend $p = 0.015$) and remained significant after also correcting for BMI and physical activity. A trend was observed between higher vegetable intake and lower disability (Fig. 1), however, this association did not attain statistical significance. We did not observe evidence of

Table 2. Association between different types of food products and overall diet quality during childhood and MS case status.

Variables consumption at age 10 (serves/week)	MS, *n*	HC, *n*	Multivariable OR[a] (95% CI)	*p* value	Multivariable OR[b] (95% CI)	*p* value
Fruit						
0–5	132	40	1	1	1	1
5–7	104	40	0.78 (0.47–1.32)	0.355	0.79 (0.47–1.34)	0.379
≥7.0	124	45	0.82 (0.49–1.36)	0.441	0.83 (0.49–1.40)	0.478
p for linear trend				0.446		0.487
Continuous			0.95 (0.86–1.05)	0.348	0.96 (0.87–1.06)	0.413
Vegetables						
0–6	106	32	1	1	1	1
6–7	116	47	0.76 (0.45–1.29)	0.312	0.75 (0.44–1.27)	0.284
≥7	138	46	0.88 (0.52–1.50)	0.647	0.86 (0.50–1.47)	0.574
p for linear trend				0.707		0.628
Continuous			0.94 (0.77–1.15)	0.553	0.93 (0.76–1.14)	0.475
Oily fish						
0	176	63	1	1	1	1
1–2	144	58	0.88 (0.57–1.34)	0.538	0.90 (0.58–1.37)	0.612
≥ 2	39	4	**3.31 (1.13–9.68)**	**0.029**	**3.26 (1.11–9.58)**	**0.032**
p for linear trend				0.230		0.221
Continuous			1.24 (0.91–1.68)	0.171	1.25 (0.92–1.69)	0.163
Red meat						
0	137	47	1	1	1	1
1–3	133	47	0.93 (0.54–1.58)	0.775	0.89 (0.52–1.52)	0.656
≥3	90	31	0.97 (0.57–1.66)	0.919	0.96 (0.56–1.64)	0.873
p for linear trend				0.951		0.922
Continuous			0.99 (0.89–1.10)	0.878	0.99 (0.89–1.10)	0.856
Whole grain bread						
0–5	119	29	1	1	1	1
5–7	83	35	0.60 (0.34–1.06)	0.076	0.57 (0.32–1.02)	0.059
≥7	157	61	0.61 (0.37–1.02)	0.059	0.62 (0.37–1.03)	0.066
p for linear trend				0.077		0.089
Continuous			**0.93 (0.88–0.99)**	**0.021**	**0.94 (0.88–0.99)**	**0.030**
Snacks, candy and fast food						
0–6	115	36	1	1	1	1
6–12	116	41	1.12 (0.68–1.83)	0.660	1.12 (0.68–1.83)	0.663
≥12	119	48	1.32 (0.79–2.19)	0.287	1.29 (0.78–2.15)	0.326
p for linear trend				0.956		0.930
Continuous			0.99 (0.95–1.03)	0.541	0.99 (0.95–1.03)	0.465
Overall diet quality score						
0–4	102	29	1	1	1	1
4–7	110	41	0.71 (0.42–1.19)	0.194	0.72 (0.43–1.23)	0.232
≥6.5	146	55	0.76 (0.45–1.27)	0.296	0.78 (0.46–1.31)	0.347
p for linear trend				0.270		0.300
Continuous			0.96 (0.87–1.06)	0.440	0.97 (0.88–1.07)	0.490

Bold values denote statistical significance at the $p < 0.05$ level.
[a]Including the following covariates: sex, sun exposure in childhood and smoking status in childhood.
[b]Including the following covariates: sex, sun exposure in childhood, smoking status in childhood, being overweight or obese in childhood and physical activity in childhood.

effect modification by sex for all analyses assessing diet and disability.

MRI volumetric measures – patients with multiple sclerosis

Associations between individual diet components and overall diet quality and MRI volumetric measures are presented in Table 3. A higher fruit intake at age 50 was consistently associated with higher MRI volumes, including MUCCA, NCGMV, NDGMV, NThalV and NCbV (Table 3), however, a significant *p* for trend was only observed for the association between fruit intake and MUCCA. Likewise, frequent consumption of vegetables was significantly associated with a higher NBV, NWMV, NCGMV, NDGMV, NThalV and lower LV.

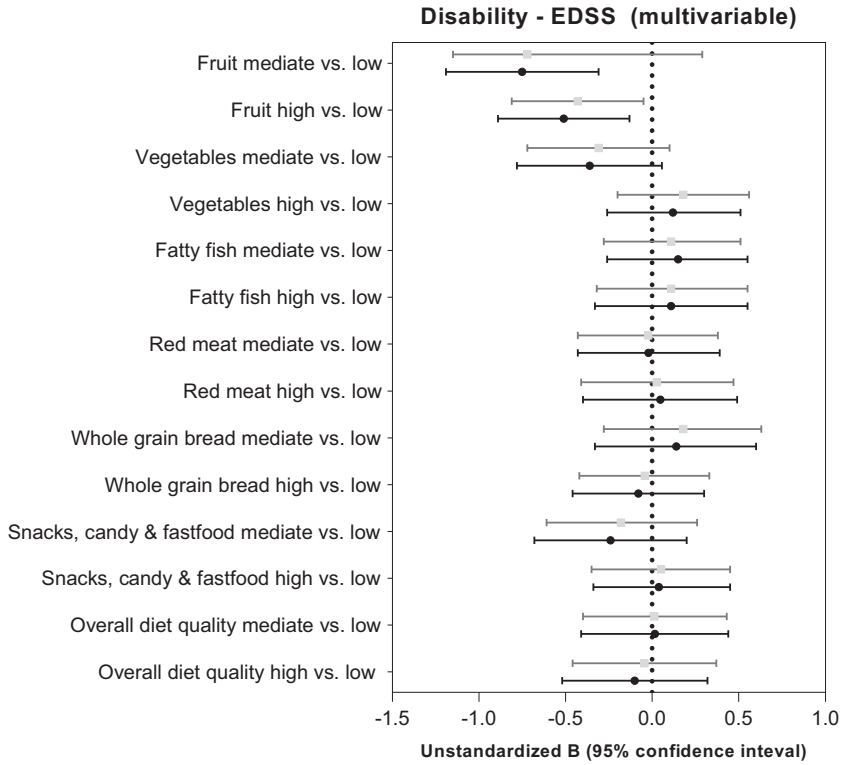

Figure 1. Multivariable analyses of the association between diet composition at age 50 and expanded disability status scale (EDSS). Visualization of multivariable analyses of the association between individual diet components and overall diet quality and the EDSS. It shows the unstandardized and 95% confidence interval of all diet components adjusted for sex, onset type, disease duration, education, disease-modifying therapy duration, sun exposure and smoking status (bullet), while the odds ratio's represented with a square are also adjusted for body mass index and physical activity.

PwMS who frequently consumed red meat had a significantly higher lesion volume (Q3 vs. Q1, multivariable (b) unst. $B = 0.3$; 95% CI 0.04–0.6, test for trend $p = 0.023$). Unexpectedly, higher consumption of snacks, candy and fast food associated with higher NCGMV, NDGMV and NCbV. We found no evidence of a significant association between oily fish intake, whole-grain bread intake and MRI volumes.

Effect modification by sex was observed for the relationship between vegetable intake and NDGMV ($p = 0.032$): in male PwMS, frequent vegetable consumption was associated with a higher NDGMV (Q3 vs. Q1, multivariable (b) unst. $B = 4.1$; 95% CI 0.1–8.0, test for trend $p = 0.033$), whereas no statistically significant association was found in female PwMS. Similarly, a different effect for each sex was observed for fruit intake and NDGMV ($p = 0.094$): higher intake of fruit (Q3 vs. Q1, multivariable (b) unst. $B = 1.7$; 95% CI 0.4–3.0, test for trend $p = 0.080$) was associated with higher NDGMV in male PwMS, but not in female PwMS.

MRI volumetric measures – healthy controls

In HC, higher fruit intake at age 50 was significantly associated with higher NCbV in the continuous model (multivariable (b) unst. $B = 0.7$; 95% CI 0.01–1.4), but not in the categorical model. In contrast to PwMS, we did not observe evidence of a significant association between vegetable consumption and LV in the HC group. Furthermore, in parallel to our observations in PwMS, HC with higher NCbV more frequently consumed candy, fast food and snacks (Q3 vs. Q1, unstd. $B = 8.3$; 95%CI 1.9–14.7, test for trend $p = 0.023$). In addition, HC with higher candy, fast food and snacks intake had a higher NCGMV and a higher NDGMV, however, no significant p for trend was observed. Furthermore, in HC, higher total diet quality was significantly associated with lower LV (multivariable (b) unst. $B = -0.06$; 95% CI -0.12 to -0.002) in the continuous model, whereas a potential trend was observed in the categorical model (Q3 vs. Q1, multivariable (b) unst. $B = -0.26$; 95% CI -0.56 to 0.039, test for trend

Table 3. Multivariable associations between individual dietary components, overall diet quality and MRI volumetric measures.

Variables		NBV		NWMV		NCGMV		NDGMV	
		Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]
Consumption at age 50 serves/week	MS, *n*	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95% CI)	Unst. B (95% CI)
Fruit									
0–5	126	1	1	1	1	1	1	1	1
5–7	91	21.6 (−4.9 to 48.0)	21.1 (−5.45 to 47.7)	0.3 (−14.8 to 15.3)	0.7 (−14.3 to 15.7)	**18.8 (1.2–36.4)***	**17.8 (0.3–35.3)***	**3.0 (1.2–4.8)****	**3.0 (1.2–4.8)*****
≥7.0	127	19.5 (−4.7 to 43.6)	18.0 (−6.8 to 42.7)	4.4 (−9.36 to 18.1)	4.9 (−9.1 to 18.8)	14.0 (−2.0 to 30.0)	11.8 (−4.4 to 28.1)	1.4 (−0.2 to 3.0)	1.5 (−0.1 to 3.2)
p for linear trend		0.126	0.169	0.518	0.481	0.106	0.179	0.137	0.101
Continuous		3.5 (−0.4 to 7.4)	3.3 (−0.8 to 7.2)	0.2 (−2.00 to 2.5)	0.4 (−1.9 to 2.6)	**3.0 (0.4–5.6)***	**2.7 (0.04–5.3)***	0.3 (−0.02 to 0.5)	**0.3 (0.01–0.6)***
Vegetable									
0–6	143	1	1	1	1	1	1	1	1
6–7	**91**	**29.5 (4.0–55.0)***	**31.2 (5.5–57.0)***	**14.7 (0.2–29.1)***	13.1 (−1.5 to 27.6)	13.6 (−3.5 to 30.7)	17.0 (−0.1 to 34.0)	**1.9 (0.1–3.6)***	**1.9 (0.1–3.7)***
≥7	127	12.8 (−10.6 to 36.2)	12.0 (−11.6 to 35.5)	−1.0 (−14.3 to 12.2)	−1.4 (−14.6 to 11.9)	13.2 (−2.5 to 28.9)	12.7 (−2.8 to 28.3)	1.0 (−0.6 to 2.6)	1.0 (−0.6 to 2.7)
p for linear trend		0.253	0.278	0.950	0.910	0.092	0.096	0.197	0.185
Continuous		8.0 (−0.7 to 16.7)	7.8 (−1.00 to 16.6)	−0.02 (−5.0 to 4.7)	−0.04 (−5.0 to 4.9)	**7.6 (1.8–13.4)***	**7.4 (1.6–13.1)***	0.5 (−0.1 to 1.1)	0.6 (−0.04 to 1.2)
Oily fish									
0	97	1	1	1	1	1	1	1	1
1–2	162	−2.9 (−27.5 to 21.6)	−4.0 (−28.6 to 20.7)	8.1 (−5.8 to 22.0)	8.5 (−5.3 to 22.4)	−9.0 (−25.4 to 7.4)	−10.5 (−26.7 to 5.7)	−1.4 (−3.1 to 0.2)	−1.4 (−3.1 to 0.3)
≥2	101	−14.1 (−41.7 to 13.5)	−16.6 (−44.7 to 11.5)	0.5 (−15.1 to 16.1)	1.1 (−14.7 to 16.8)	−12.7 (−31.2 to 5.7)	−15.8 (−34.2 to 2.7)	−1.0 (−2.8 to 0.9)	−0.9 (−2.8 to 1.0)
p for linear trend		0.310	0.240	0.973	0.917	0.177	0.094	0.335	0.381
Continuous		−4.1 (−14.4 to 6.2)	−5.1 (−15.7 to 5.4)	1.7 (−4.5 to 7.2)	1.6 (−4.4 to 7.5)	−4.8 (−11.6 to 2.1)	−6.0 (−12.9 to 0.9)	−0.3 (−1.0 to 0.4)	−0.3 (−1.0 to 0.4)
Red meat									
0	88	1	1	1	1	1	1	1	1
1–3	160	−8.2 (−33.5 to 17.0)	−7.2 (−32.7 to 18.3)	−1.21 (−15.5 to 13.1)	−1.1 (−15.5 to 13.2)	−6.4 (−23.3 to 10.5)	−5.4 (−22.2 to 11.4)	0.3 (−1.5 to 2.0)	0.2 (−1.5 to 2.0)
≥3	112	−8.7 (−36.6 to 19.2)	−7.9 (−36.0 to 20.2)	−0.8 (−16.7 to 15.0)	−1.9 (−17.7 to 13.9)	−7.2 (−25.8 to 11.5)	−5.3 (−23.8 to 13.3)	0.2 (−1.7 to 2.1)	0.2 (−1.7 to 2.1)
p for linear trend		0.557	0.593	0.925	0.811	0.466	0.597	0.854	0.884
Continuous		−2.19 (−8.7 to 4.3)	−2.1 (−8.6 to 4.5)	−0.4 (−4.1 to 3.3)	−0.7 (−4.4 to 3.0)	−1.6 (−5.9 to 2.8)	−1.2 (−5.6 to 3.1)	−0.01 (−0.5 to 0.4)	−0.01 (−0.5 to 0.4)

(*Continued*)

Table 3 Continued.

Variables		NBV		NWMV		NCGMV		NDGMV	
		Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]	Multivariable[a]
Consumption at age 50 serves/week	MS, *n*	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95% CI)	Unst. B (95% CI)
Whole-grain bread									
0–5	104	1	1	1	1	1	1	1	1
5–7	79	−9.88 (−37.2 to 17.4)	−9.3 (−36.71 to 18.2)	−5.3 (−20.7 to 10.2)	−5.7 (−21.1 to 9.7)	−4.2 (−22.5 to 14.1)	−3.1 (−21.2 to 15.0)	−0.4 (−2.3 to 1.2)	−0.5 (−2.3 to 1.4)
≥7	177	−3.66 (−27.0 to 19.7)	−5.00 (−28.61 to 18.7)	−4.5 (−17.7 to 8.8)	−5.0 (−18.3 to 8.3)	1.2 (−14.4 to 16.8)	0.5 (−15.1 to 16.1)	−0.5 (−2.1 to 1.1)	−0.4 (−2.0 to 1.2)
*p*for linear trend		0.811	0.715	0.534	0.481	0.825	0.992	0.578	0.630
Continuous		−1.4 (−12.0 to 10.2)	−2.2 (−14.0 to 9.6)	−2.1 (−8.6 to 4.5)	−2.4 (−9.0 to 4.3)	0.9 (−6.9 to 8.6)	0.4 (−7.4 to 8.2)	−0.2 (−1.0 to 0.6)	−0.2 (−1.0 to 0.6)
Snacks, candy and fast food									
0–6	93	1	1	1	1	1	1	1	1
6–12	106	2.7 (−24.3 to 29.6)	2.07 (−25.1 to 29.3)	−1.7 (−17.1 to 13.6)	−2.8 (−18.2 to 12.6)	3.4 (−14.5 to 21.3)	3.9 (−13.9 to 21.6)	1.0 (−0.8 to 2.9)	1.1 (−0.8 to 2.9)
≥12	160	17.6 (−7.5 to 42.6)	17.59 (−7.7 to 42.9)	−2.0 (−16.3 to 12.3)	−3.6 (−17.9 to 10.7)	**17.5 (0.8–34.1)***	**19.1 (2.6–35.6)***	**1.8 (0.1–3.5)***	**1.8 (0.1–3.5)***
p for linear trend		0.134	0.134	0.793	0.633	**0.027**	**0.015**	**0.044**	**0.043**
Continuous		1.2 (−1.2 to 3.7)	1.25 (−1.2 to 3.7)	−0.2 (−1.6 to 1.1)	−0.4 (−1.8 to 1.0)	1.3 (−0.3 to 2.9)	1.5 (−0.1 to 3.1)	**0.2 (0.01–0.3)***	**0.2 (0.01–0.3)***
Overall diet quality score[a]									
0–4	98	1	1	1	1	1	1	1	1
4–7	120	13.8 (−11.6 to 39.1)	12.6 (−12.9 to 38.1)	1.67 (−12.7 to 16.0)	2.6 (−11.7 to 17.0)	11.7 (−5.2 to 28.5)	9.5 (−7.3 to 26.2)	0.9 (−0.8 to 2.7)	1.0 (−0.8 to 2.7)
≥6.5	141	−3.9 (−29.4 to 21.6)	−6.6 (−32.7 to 19.5)	−3.7 (−18.1 to 10.7)	−2.6 (−17.3 to 12.1)	0.7 (−16.2 to 17.7)	−3.2 (−20.3 to 13.9)	−0.5 (−2.3 to 1.2)	−0.5 (−2.2 to 1.3)
p for linear trend		0.707	0.569	0.594	0.704	0.991	0.664	0.497	0.567
Continuous		0.6 (−4.2 to 5.4)	0.07 (−4.9 to 5.0)	0.18 (−2.5 to 2.88)	0.4 (−2.4 to 3.1)	0.6 (−2.6 to 3.8)	−0.1 (−3.4 to 3.1)	−0.5 (−0.4 to 0.3)	−0.02 (−0.4 to 0.3)

Table 3 Continued.

Variables Consumption at age 50 serves/week		NThalV Multivariable[a] Unst. B (95%CI)	Multivariable[a] Unst. B (95%CI)	NCbV Multivariable[a] Unst. B (95%CI)	Multivariable[a] Unst. B (95% CI)	MUCCA Multivariable[a] Unst. B (95% CI)	Multivariable[a] Unst. B (95%CI)	LV Multivariable[a] Unst. B (95%CI)	Multivariable[a] Unst. B (95%CI)
Fruit									
0–5	126	1	1	1	1	1	1	1	1
5–7	91	**0.7 (0.04–1.4)***	**0.7 (0.06–1.4)***	**5.3 (0.7–9.9)***	**5.1 (0.5–9.7)***	**4.7 (0.5–8.8)***	**4.7 (0.5–8.9)***	−0.1 (−0.3 to 0.2)	−0.1 (−0.3 to 0.2)
≥7.0	127	0.4 (−0.2 to 1.0)	0.4 (−0.2 to 1.1)	2.9 (−1.2 to 7.1)	2.6 (−1.7 to 6.8)	**5.4 (1.6–9.3)****	**5.5 (1.6–9.4)****	−0.1 (−0.3 to 0.2)	−0.1 (−0.3 to 0.2)
p for linear trend		0.230	0.202	0.223	0.287	**0.007**	**0.007**	0.613	0.612
Continuous		0.1 (−0.02 to 0.2)	0.1 (−0.01 to 0.2)	0.5 (−0.2 to 1.2)	0.6 (−0.2 to 1.2)	**0.8 (0.1–1.4)***	**0.8 (0.5–1.4)***	−0.01 (−0.1 to 0.03)	−0.01 (−0.1 to 0.03)
Vegetables									
0–6	143	1	1	1	1	1	1	1	1
6–7	**91**	**0.7 (0.03–1.2)***	**0.6 (−0.05–1.2)***	0.9 (−3.7 to 5.4)	1.4 (−3.1 to 6.0)	1.7 (−2.5 to 5.8)	1.6 (−2.6 to 5.8)	**−0.3 (−0.5 to 0.01)***	**−0.3 (−0.5 to 0.01)***
≥7	127	0.3 (−0.3 to 0.9)	0.3 (−0.3 to 0.9)	0.8 (−3.3 to 5.0)	0.8 (−3.4 to 4.9)	0.03 (−3.8 to 3.8)	−0.1 (−3.9 to 3.8)	−0.2 (−0.4 to 0.03)	−0.2 (−0.4 to 0.03)
p for linear trend		0.243	0.258	0.686	0.697	0.960	0.996	0.072	0.073
Continuous		0.2 (−0.1 to 0.4)	0.2 (−0.1 to 0.4)	0.8 (−0.7 to 2.4)	0.8 (−0.7 to 2.3)	0.2 (−1.3 to 1.6)	0.1 (−1.3 to 1.6)	**−0.1 (−0.2 to 0.00)***	**−0.1 (−0.2 to 0.00)***
Oily fish									
0	97	1	1			1	1	1	1
1–2	162	−0.3 (−0.9 to 0.3)	−0.3 (−0.6 to 0.7)	−1.8 (−6.1 to 2.5)	−2.0 (−6.3 to 2.3)	−1.4 (−5.3 to 2.6)	−1.4 (−5.4 to 2.5)	−0.002 (−0.2 to 0.2)	−0.002 (−0.2 to 0.2)
≥2	101	−0.3 (−1.0 to 0.5)	−0.2 (−1.0 to 0.4)	−0.4 (−5.2 to 4.0)	−0.8 (−5.7 to 4.1)	−2.6 (−7.1 to 1.8)	−2.8 (−7.2 to 1.7)	0.1 (−0.2 to 0.4)	0.1 (−0.2 to 0.4)
p for linear trend		0.479	0.381	0.893	0.759	0.243	0.218	0.409	0.401
Continuous		−0.1 (−0.3 to 0.2)	−0.1 (−0.3 to 0.2)	−0.2 (−2.0 to 1.6)	−0.4 (−2.0 to 1.4)	−1.4 (−3.0 to 0.3)	−1.5 (−3.2 to 0.18)	0.04 (−0.1 to 0.1)	0.04 (−0.1 to 0.1)
Red meat									
0	88	1	1	1	1	1	1	1	1
1–3	160	0.00 (−0.7 to 0.7)	0.00 (−0.7 to 0.7)	2.4 (−2.1 to 6.8)	2.5 (−1.9 to 6.9)	**5.0 (1.0–9.0)***	**5.1 (1.1–9.2)***	0.1 (−0.1 to 0.4)	0.1 (−0.1 to 0.4)
≥3	112	−0.3 (−1.0 to 0.5)	−0.3 (−1.0 to 0.5)	0.9 (−4.0 to 5.7)	1.2 (−3.7 to 6.1)	3.7 (−0.7 to 8.2)	3.7 (−0.7 to 8.2)	**0.3 (0.04–0.6)***	**0.3 (0.04–0.6)***
p for linear trend		0.466	0.383	0.794	0.383	0.134	0.138	**0.022**	**0.023**
Continuous								**0.1 (0.003–0.1)***	**0.1 (0.003–0.1)***

(*Continued*)

Table 3 Continued.

Variables		NThalV Multivariable[a]	Multivariable[a]	NCbV Multivariable[a]	Multivariable[a]	MUCCA Multivariable[a]	Multivariable[a]	LV Multivariable[a]	Multivariable[a]
Consumption at age 50 serves/week		Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95% CI)	Unst. B (95% CI)	Unst. B (95%CI)	Unst. B (95%CI)	Unst. B (95%CI)
		−0.10 (−0.3 to 0.1)	−0.10 (−0.3 to 0.1)	−0.2 (−1.4 to 0.9)	−0.2 (−1.3 to 0.9)	0.7 (−0.3 to 1.8)	0.7 (−0.3 to 1.8)		
Whole-grain bread									
0–5	104	1	1	1	1	1	1	1	1
5–7	79	−0.2 (−0.9 to 0.5)	−0.2 (−0.9 to 0.5)	−0.04 (−4.8 to 4.7)	−0.1 (−4.6 to 4.9)	−2.7 (−7.0 to 1.7)	−2.7 (−7.1 to 1.7)	0.1 (−0.2 to 0.4)	0.1 (−0.2 to 0.4)
≥7	177	−0.1 (−0.7 to 0.5)	−0.1 (−0.7 to 0.5)	0.02 (−4.1 to 4.1)	0.1 (−4.2 to 4.0)	0.5 (−3.2 to 4.3)	0.5 (−3.3 to 4.2)	−0.03 (−0.3 to 0.2)	−0.03 (−0.3 to 0.2)
p for linear trend		0.806	0.753	0.990	0.963	0.656	0.716	0.720	0.723
Continuous		−0.04 (−0.3 to 0.3)	−0.05 (−0.4 to 0.3)	0.1 (−2.0 to 2.0)	0.1 (−2.1 to 2.0)	0.4 (−1.4 to 2.3)	0.4 (−1.5 to 2.2)	−0.02 (−0.1 to 0.09)	−0.02 (−0.1 to 0.09)
Snacks, candy and fast food									
0–6	93	1	1	1	1	1	1	1	1
6–12	106	0.5 (−0.2 to 1.2)	0.5 (−0.2 to 1.2)	3.9 (−0.8 to 8.6)	4.1 (−0.6 to 8.7)	3.2 (−1.1 to 7.6)	3.1 (−1.3 to 7.5)	−0.02 (−0.3 to 0.2)	−0.02 (−0.3 to 0.2)
≥12	160	0.6 (−0.1 to 1.2)	0.5 (−0.1 to 1.2)	**6.2 (1.9–10.5)****	**6.2 (2.2–10.9)****	2.9 (−1.1 to 6.9)	2.8 (−1.27 to 6.9)	0.01 (−0.2 to 0.3)	0.01 (−0.2 to 0.3)
p for linear trend		0.112	0.161	**0.006**	**0.003**	0.206	0.231	0.886	0.883
Continuous		0.1 (−0.01–0.1)	0.1 (−0.01–0.1)	**0.7 (0.3–1.1)****	**0.7 (0.3–1.2)*****	0.2 (−0.2 to 0.6)	0.2 (−0.2 to 0.6)	−0.001 (−0.2 to 0.2)	−0.001 (−0.2 to 0.2)
Overall diet quality score[a]									
0–4	98	1	1	1	1	1	1	1	1
4–7	120	0.3 (−0.4 to 0.9)	0.3 (−0.4 to 1.0)	3.0 (−1.4 to 7.4)	2.5 (−1.9 to 6.9)	−1.2 (−5.2 to 2.9)	−1.2 (5.3 to 2.9)	**−0.3 (−0.5 to −0.02)***	**−0.3 (−0.5 to −0.02)***
≥6.5	141	−0.1 (−0.7 to 0.6)	−0.1 (−0.7 to 0.6)	−1.7 (6.1–2.7)	−2.5 (7.0–1.9)	−0.2 (−4.3 to 3.9)	−0.3 (−4.5 to 3.9)	−0.2 (0.4–0.06)	−0.19 (−0.4 to 0.1)
p for linear trend		0.791	0.866	0.390	0.232	0.940	0.903	0.162	0.160
Continuous		0.02 (−0.1 to 0.1)	0.02 (−0.1 to 0.2)	−0.2 (−1.1 to 0.6)	−0.4 (−1.2 to 0.5)	−0.1 (−0.8 to 0.7)	−0.1 (−0.9 to 0.7)	−0.04 (−0.1 to 0.01)	−0.04 (−0.1 to 0.02)

Bold values denote statistical significance at the $p < 0.05$ level; *p value <0.05; **p value <0.01; ***p value <0.001.

[a]Including the following covariates: sex, sun exposure at age 50, smoking status, disease duration since onset, disease-modifying therapy duration, onset type, education, body mass index (BMI) and physical activity at age 50.

$p = 0.077$). No evidence of effect modification by sex was found in the HC group.

Discussion

In our nationwide population-based retrospective cohort of PwMS and HCs of the same birth year, we demonstrate that overall diet quality and individual dietary components during childhood were associated with adult-onset MS and onset type, but not with age of onset. Furthermore, we showed consistent associations between individual dietary components at age 50, particularly fruit and vegetables, and disability (EDSS) and MRI volumetric measures, with distinct patterns in PwMS and HC. Associations of individual food products solely found in PwMS may indicate a MS-specific effect. However, overall diet quality at age 50 only appeared to associate with lower lesion volume in PwMS, which was also observed in HC.

In light of discussing and interpreting our findings, it should first be mentioned that our study is prone to certain types of bias which prevent us from drawing strong conclusions. Most importantly, our retrospective cohort study introduced the potential for inaccurate recall of diet and risk factors in early life. Nevertheless, similar studies examining the relationship between early life exposure to environmental factors and disease onset later in life often deal with this limitation, and therefore, we largely rely on studies with such limitations. Second, this study used dietary questionnaires that not have been validated and therefore results must be interpreted with caution, given the potential for measurement error (i.e. information bias). Third, participants may have over- or under-reported dietary components as they may have had a preconceived notion that certain food types are associated with MS disease outcome (i.e. recall bias). Last, although most HC was recruited through various media channels, some HC were recruited via PwMS, which may have introduced selection bias. Therefore, in the present study, we do not aim to make any definitive claims based on our results. Nonetheless, our nationwide population-based birth-year cohort study provides valuable insights to improve our understanding of the association between diet and MS and provides relevant clues to guide future research on this topic.

We found that PwMS who consumed higher amounts of fruit had less severe disability (EDSS) and higher NCGMV and NDGMV compared to those who consumed fewer. Furthermore, our study supports significant consistent associations between vegetable consumption at age 50 and higher MRI-derived brain volumes (NBV, NWM, NCGMV and NThalV) and lower LV. Our findings parallel the HOLISM (Health Outcomes in a Sample of people with MS) study which demonstrated that higher consumption of fruit and vegetables was associated with lower levels of patient-reported disease activity and disability.[29,30] In addition, greater adherence to vegetables (not including green-leafy vegetables) were the only individual MIND diet components which associated with higher thalamic volumes, although marginally.[11] The possible beneficial effects of fruit and vegetables have been attributed to the presence of antioxidants, such as polyphenols, that have antioxidant, anti-inflammatory and immunomodulatory properties.[31,32] This could also explain our observation that frequent fruit intake during childhood was less prevalent in patients with a relapsing onset compared to patients with a primary progressive onset, as relapsing-remitting MS is characterized by focal inflammatory demyelinating white matter lesions with profound blood–brain–barrier (BBB) leakage.[33] Importantly, associations between fruit and vegetables and MRI metrics were solely found in PwMS.

Increasing reports suggest that diets high in fish omega-3-oily acid, up to 5 years before diagnosis/onset, decreases the risk of MS,[34–37] although not all studies showed positive relations. In two studies, recent fish consumption[38] and fish consumption in childhood and young adulthood[15] were not related to MS prevalence. However, unexpectedly, we observed a higher intake of oily fish at childhood in PwMS compared to HC. Results should be interpreted with caution, as our observations could be true associations or due to recall bias or interrelations with other food products that have not been taken into account in the current study. While fish intake has previously been linked to lower cerebrovascular disease burden[39] and larger grey matter volumes in cognitively normal elders,[40] we found no associations between oily fish consumption and MRI volumes in PwMS nor in HC. Future large cohort studies are needed to critically assess the relationship between fish consumption and MS onset and course.

While red meat consumption, especially processed red meat, has been linked to increased risk of chronic diseases such as cardiovascular disease,[41] obesity[42] and (colorectal) cancer,[43] studies in MS have been inconsistent.[38,44–46] Absent relations with MS onset have been reported,[38] while higher non-processed red meat consumption 1-year preceding diagnosis was associated with a reduced risk of CNS demyelination.[45] One imaging study showed absent associations between red and processed meats and ThalV, LV, GMV and normal-appearing white matter.[11] In contrast, meat consumption showed a prospective association with disability progression[47] and a cross-sectional association with worse disability in MS patients.[8] In our cohort, at childhood age and age 50, no statistically significant

associations were observed between red meat consumption and MS outcome measures. However, we did observe an association between frequent red meat consumption and higher LV in PwMS. Red meat has been linked to a potentially detrimental effect on the brain due to its high content of saturated fat and cholesterol, advanced glycation endproducts produced in cooked meat and high amounts of heme iron leading to iron-mediate oxidative stress.[48–50] In addition, red and processed meat consumption has been associated with hypertension and increased risk of (ischemic) stroke.[51,52]

In our cohort, MS was less prevalent among individuals who frequently consumed whole-grain bread during childhood. The few studies that have been conducted on the relationship between diet in early life and adult-onset MS reported that higher consumption of foods that are considered healthy, such as yoghurt, fruit, vegetables[15,16] and fish[16,36] are associated with a reduced probability of adult-onset MS. The only study including whole-grain products reported absent associations with MS prevalence.[15] Nevertheless, a recent study found that adult MS patients who frequently consumed whole grains were at lower odds of severe versus mild disability.[8] Also, a growing body of evidence demonstrates the ability of whole-grain intake to reduce systemic inflammation.[53] The mechanism behind this protective effect may involve whole grain-induced effects on the gut microbiome: short-chain oily acids (SCFAs) derived from dietary fibre fermentation by gut microbiota may regulate immune responses and the composition of the intestinal microbiota.[30] As we could not observe associations between whole-grain bread at age 50 and MRI volumes and disability in PwMS, results warrant further exploration in studies including a broad range of whole-grain products.

While previous studies have linked a healthier adult diet with higher thalamic volume[11] and less severe disability,[8,29] we did not identify significant associations between overall diet quality at childhood and age 50 and MS metrics. However, we did observe that male PwMS had a lower diet quality and higher intake of candy, fast food and snacks as a child compared to HC, and we noted a significant association between overall diet quality and LV in both PwMS and HC. Absent associations could be true associations or due to the fact that our diet quality score consisted of relatively few dietary components and relied on the allocations of a score per food item. Moreover, the paradoxical positive associations between intake of snacks, candy and fast food at age 50 and several MRI volumes in both PwMS and HC could have influenced our results. Although these associations persisted after adjusting for BMI, it is tempting to speculate that these associations could be linked to pathological lipid accumulation in the brain and do not reflect the preservation of healthy brain tissue.[54] Nevertheless, results should be cautiously interpreted and future studies are warranted to critically assess the effect of snacks, candy and fast food.

Sexual dimorphism, such as is observed in the relationship between childhood/adolescent obesity and MS risk,[12,55] was found in several association between dietary measures and MS metric. Due to the high female-to-male sex ratio in MS reflected in our cohort, the male sample size was inevitably small and relations may have therefore not been detected. However, we did find significant associations between fruit and vegetable consumption and NDGMV in male PwMS, but not in female PwMS. Fundamental hormonal and physiological sex-based differences are important factors that may cause a different response to nutrients in male and female individuals.[56] Moreover, male and female individuals may possess different nutritional needs.[57] Therefore, future studies should not only adjust for sex but also explore sex interaction.

The most important characteristic of our population-based study is the inclusion of patients and HCs of the same birth year. Therefore, our cohort was unbiased by dietary trends and period effects. In addition, by including PwMS and HC from the same age, the discrepancy between associations found in PwMS and HC could not be attributable to physiological age effects. Our study has several limitations, as already addressed in the second paragraph of this discussion. In addition, the range of dietary components was limited as was detailed information on food products, such as processed versus unprocessed meat and caloric intake. Although we were able to detect several associations between diet and MS, the inclusion of participants solely from the Netherlands might have further limited the heterogeneity of dietary patterns. Second, results could be attributable to other inter-related nutritional components, vitamin D status or supplementation, blood lipid anomalies, socio-economic status or other lifestyle factors that have not been taken into account in the current study. Third, associations were corrected for the MS subtype, however, we did not explore effect modification by the MS subtype. Lastly, data on diet during adolescence and time exposed to dietary components were not available.

In summary, in our cohort unbiased by age, we observed associations between dietary factors in childhood and the development of MS and onset type. Furthermore, we show consistent associations between dietary factors at age 50 and disability and MRI volumes. Although these findings should be cautiously interpreted, our results could help to design future longitudinal and interventional (imaging)studies, which would be better suited to investigate causality and which are needed for dietary recommendations for PwMS and clinicians.

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Author Contributions

Floor Loonstra: Conceptualization, formal analysis, investigation, project administration, methodology, writing – original draft preparation, writing – review & editing. **Reinier de Ruiter:** Investigation, project administration, writing – review and editing. **Eva Strijbis:** Writing – review and editing. **Menno Schoonheim:** Writing – review and editing. **Bastiaan Moraal:** Writing – review and editing. **Brigit de Jong:** Methodology, writing – review and editing. **Bernard Uitdehaag:** Conceptualization, funding acquisition, supervision, writing – review and editing.

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Conflict of Interest

F.C. Loonstra, L.R.J. de Ruiter, B. Moraal, E.M.M. Strijbis, B.A. de Jong report no disclosures. M.M. Schoonheim serves on the editorial board of Neurology and Frontiers in Neurology, receives research support from the Dutch MS Research Foundation and Amsterdam Neuroscience and has served as a consultant for or received research support and/or speaker honoraria from Atara Biotherapeutics, Biogen, Celgene, Genzyme, MedDay and Merck. B.M.J. Uitdehaag received consultancy fees from Biogen Idec, Genzyme, Merck Serono, Novartis, Roche, Teva and Immunic Therapeutics.

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